BASIC CLINICAL RADIOBIOLOGY

Alfredo Polo MD, PhD

Applied Radiation Biology and Radiotherapy Section
Division of Human health
BASIC RADIATION DAMAGE
SINGLE STRAND BREAK (SSB)
REPAIR MECHANISM

Direct (direct ionization) DNA damage

Indirect (free radical-mediated) DNA damage

5' C T A C G G T C T T
3' G A T G C C A G A T G A T A C C

hydrogen bonded base pairs

NUCLEASE

5' C T A C G G T C T T
3' G A T G C C A G A T G A T A C C

DNA HELICASE

5' C G G T C T T
3' G A T G C C A G A T G A T A C C

DNA helix with 12 nucleotide gap

DNA POLYMERASE PLUS DNA LIGASE

5' C T A C G G T C T A C T A T G G
3' G A T G C C A G A T G A T A C C

Alberts B. Molecular biology of the cell. 1994
DOUBLE STRAND BREAK (DSB) REPAIR MECHANISM

Direct (direct ionization) DNA damage

Indirect (free radical-mediated) DNA damage

Sensor proteins
Rad9-Rad1-Hus1

Upstream kinases
ATR, ATM, Chk2

Mediators/regulators
M/R/N, BRCA1, p53

Effector proteins

Cell-cycle response

Apoptotic response

HR
Rad51 and paralogues, BRCA2, Rad52, Rad54, XRCC2, XRCC3

NHEJ
Ku70, Ku86, DNA-PKcs, Artemis, XRCC4, LigaseIV

Willers H, et al. BJ Cancer 2004
INSIDE A FRACTION

![Graph showing INSIDE A FRACTION with axes for Value (%) and Fraction time (%). The graph includes various data points and lines for DOSE, Linear(DOSE), DAMAGE, Log(DAMAGE), REPAIR, and Expon(REPAIR).]
LINEAR QUADRATIC MODEL
NSD: Nominal standard dose (Ellis, 1969)
TDF: time-dose-fractionation (Orton & Ellis, 1973)
ERD: extrapolated response dose (Barendsen, 1982)
LQ: linear-quadratic (Orton & Cohen, 1988)
α: Parameter that express single-hit/lethal (linear component). Value in Gy$^{-1}$

β: Parameter that express multiple-hit/sublethal damage (quadratic component). Value in Gy$^{-2}$

α/β: Proportion between lethal and sublethal damage. Value in Gy
The much smaller proportion at 2 Gy than 8 Gy per fraction is showed.

Only the red proportion is altered by $\alpha/\beta$, $T_{1/2}$ and dose per fraction.

Keeping low the dose per fraction guarantees minimal risk of excess damage in late tissues.

Adapted from Fowler 1999
Adapted from Fowler 1999

BETWEEN FRACTIONS

- Creation of SLD
- Repair of SLD

Adapted from Fowler 1999
SUBLETHAL DAMAGE REPAIR: incomplete repair

1. Conventional EBRT/HDR daily fractions (>24h) permit enough time between fractions for full repair to occur.

2. If interfraction time is reduced to less than approx 8h, repair between fraction may be incomplete and cell survival decreased.

3. A potential for therapeutic gain exists when the fractionation sensitivity $\alpha/\beta$ for the host dose limiting late reacting normal tissues is greater than a tumor lying within such tissue.

Thames HD et al. Incomplete repair model for survival after fractionated and continuous irradiation. IJRO 1985; 47: 319

Dale RG et al. The application of the LQ formula dose-effect equation to fractionated and protracted radiotherapy. B J Radiol 1985; 58: 515

ENDOTHELIAL MEDIATED CELL DAMAGE
BASIC MODEL FOR ISOEFFECT CALCULATION
A SIMPLE METHOD OF OBTAINING EQUIVALENT DOSES FOR USE IN HDR BRACHYTHERAPY

SUBIR NAG, M.D., AND NILENDU GUPTA, PH.D.

Division of Radiation Oncology, Arthur G. James Cancer Hospital and Research Institute, Ohio State University, Columbus, OH

\[
\text{BED} = nd \left[ 1 + \frac{d}{(\alpha/\beta)} \right] \quad (1)
\]

\[
D_{\text{Eq}} = \frac{\text{BED}}{\left(1 + \frac{d_{\text{REF}}}{(\alpha/\beta)}\right)} \quad (2)
\]
The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction

David J. Brenner, PhD, DSc

The tool most commonly used for quantitative predictions of dose/fractionation dependencies in radiotherapy is the mechanistically based linear-quadratic (LQ) model. The LQ formalism is now almost universally used for calculating radiotherapeutic isoeffect doses for different fractionation/protraction schemes. In summary, the LQ model has the following useful properties for predicting isoeffect doses: (1) it is a mechanistic, biologically based model; (2) it has sufficiently few parameters to be practical; (3) most other mechanistic models of cell killing predict the same fractionation dependencies as does the LQ model; (4) it has well-documented predictive properties for fractionation/dose-rate effects in the laboratory; and (5) it is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction. To date, there is no evidence of problems when the LQ model has been applied in the clinic.

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ESTRO project

Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology

Richard Pötter\textsuperscript{a,\,*}, Christine Haie-Meder\textsuperscript{b}, Erik Van Limbergen\textsuperscript{c}, Isabelle Barillot\textsuperscript{d}, Marisol De Brabandere\textsuperscript{c}, Johannes Dimopoulos\textsuperscript{a}, Isabelle Dumas\textsuperscript{b}, Beth Erickson\textsuperscript{e}, Stefan Lang\textsuperscript{a}, An Nulens\textsuperscript{c}, Peter Petrow\textsuperscript{f}, Jason Rownd\textsuperscript{e}, Christian Kirisits\textsuperscript{a}

\textsuperscript{a}Department of Radiotherapy and Radiobiology, Medical University of Vienna, Austria, \textsuperscript{b}Department of Radiotherapy, Brachytherapy Unit, Institut Gustave Roussy, Villejuif, France, \textsuperscript{c}Department of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium, \textsuperscript{d}Department of Radiation Oncology, Centre George-Francois Leclerc, Dijon, France, \textsuperscript{e}Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA, \textsuperscript{f}Service de Radiodiagnostic, Institut Curie, Paris, France
# EXAMPLE: HDR BRACHYTHERAPY FOR CERVICAL CANCER

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>Point A (Physical dose)</th>
<th>Point A (Equivalent dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT</td>
<td>25fr x 1.8Gy (45 Gy)</td>
<td>44 Gy EQD2 (a/β=10)</td>
</tr>
<tr>
<td>BT</td>
<td>4fr x 7Gy (28 Gy)</td>
<td>40 Gy EQD2 (a/β=10)</td>
</tr>
<tr>
<td>Total</td>
<td>73 Gy</td>
<td>84 Gy EQD (a/β=10)</td>
</tr>
</tbody>
</table>
**EXAMPLE: HDR BRACHYTHERAPY FOR CERVICAL CANCER**

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</thead>
<tbody>
<tr>
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<td>44 Gy EQD2 ($\alpha/\beta=10$)</td>
</tr>
<tr>
<td>BT</td>
<td>4fr x 7Gy (28 Gy)</td>
<td>40 Gy EQD2 ($\alpha/\beta=10$)</td>
</tr>
<tr>
<td>Total</td>
<td>73 Gy</td>
<td>84 Gy EQD ($\alpha/\beta=10$)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OAR</th>
<th>Dose to OAR (Physical dose)</th>
<th>Dose to OAR (Equivalent dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT</td>
<td>25fr x 1.8Gy (45 Gy)</td>
<td>43 Gy EQD2 ($\alpha/\beta=3$)</td>
</tr>
<tr>
<td>BT</td>
<td>4fr x 4.9Gy (70% of PtA) (20 Gy)</td>
<td>31 Gy EQD2 ($\alpha/\beta=3$)</td>
</tr>
<tr>
<td>Total</td>
<td>65 Gy</td>
<td>74 Gy EQD ($\alpha/\beta=3$)</td>
</tr>
</tbody>
</table>
Ogino I, et al. Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. IJRO 1995; 31: 725

BED < 119 keeps rectal G3-4 < 5%
BED < 124 keeps rectal G3-4 < 10%
Table 2. Probability of G2–G4 side effects according to dose levels

<table>
<thead>
<tr>
<th>Dose volume</th>
<th>5%</th>
<th>10%</th>
<th>20%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D_{2cc}</td>
<td>67 (30–79)</td>
<td>78 (66–110)</td>
<td>90 (78–171)</td>
<td>0.0178</td>
</tr>
<tr>
<td>D_{1cc}</td>
<td>71 (0–89)</td>
<td>87 (69–209)</td>
<td>104 (87–443)</td>
<td>0.0352</td>
</tr>
<tr>
<td>D_{0.1cc}</td>
<td>83</td>
<td>132</td>
<td>186</td>
<td>0.1364</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D_{2cc}</td>
<td>70 (0–95)</td>
<td>101 (29–137)</td>
<td>134 (110–371)</td>
<td>0.0274</td>
</tr>
<tr>
<td>D_{1cc}</td>
<td>71 (0–107)</td>
<td>116 (17–169)</td>
<td>164 (129–498)</td>
<td>0.0268</td>
</tr>
<tr>
<td>D_{0.1cc}</td>
<td>61* (0–155)</td>
<td>178 (0–368)</td>
<td>305 (213–2126)</td>
<td>0.0369</td>
</tr>
</tbody>
</table>

Abbreviation: CI = confidence interval.
Probability analyses for G2–G4 side effects according to dose levels for D_{2cc}, D_{1cc}, and D_{0.1cc} using probit.
* lower level due to broad CI.

Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

Fig. 2. Relationship between D_{2cc} and late side effects in the urinary bladder.


Fig. 1. Dose–response relationships (D90 in the HR CTV) for local control in the total patient population (left panel), for group 2 (large tumours, middle panel) and for group 2b (large, non-responding tumours, right panel). Particular values of the curves are presented in Table 3.

Table 3
Dose–response parameter for D90 and D100 of the HR CTV and the IR CTV for the tumour categories for which a significant dose–effect was observed.

<table>
<thead>
<tr>
<th>Tumour group</th>
<th>ED50 [95% CI]</th>
<th>ED70 [95% CI]</th>
<th>ED80 [95% CI]</th>
<th>ED90 [95% CI]</th>
<th>y-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D90 HR CTV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>61 [22;70]</td>
<td>72 [57.82]</td>
<td>80 [71.97]</td>
<td>92 [82;131]</td>
<td>1.1</td>
</tr>
<tr>
<td>2b</td>
<td>68 [30.78]</td>
<td>77 [67;118]</td>
<td>83 [74;137]</td>
<td>91 [80;228]</td>
<td>2.0</td>
</tr>
<tr>
<td>Total</td>
<td>45 [0;60]</td>
<td>61 [21;72]</td>
<td>71 [50;81]</td>
<td>86 [77;113]</td>
<td>0.6</td>
</tr>
<tr>
<td>D100 HR CTV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>54 [41;58]</td>
<td>59 [53;64]</td>
<td>63 [59;70]</td>
<td>68 [64;83]</td>
<td>0.5</td>
</tr>
<tr>
<td>2b</td>
<td>56 [0;63]</td>
<td>62 [55;123]</td>
<td>66 [60;197]</td>
<td>72 [64;214]</td>
<td>1.9</td>
</tr>
<tr>
<td>Total</td>
<td>33 [0;47]</td>
<td>46 [0;55]</td>
<td>55 [17;63]</td>
<td>67 [59;103]</td>
<td>1.9</td>
</tr>
<tr>
<td>D90 IR CTV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>53 [21;59]</td>
<td>60 [48;66]</td>
<td>65 [59;76]</td>
<td>71 [66;102]</td>
<td>1.6</td>
</tr>
<tr>
<td>D100 IR CTV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>47 [21;51]</td>
<td>52 [42;55]</td>
<td>55 [51;62]</td>
<td>59 [56;81]</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Dose effect parameters have been calculated by probit analyses (EDxx: dose, at which cure can be expected in xx% of the patients; CI, confidence interval; y, normalized dose–response gradient [20]).
CONCLUSIONS